REMARKS

Applicant respectfully requests reconsideration of this application in view of the foregoing amendments and the following remarks.

I. Status of the Claims

Claims 26, 28 and 39 are amended to recite specific embodiments. Support for these claims is found throughout the application as filed. These amendments are made without prejudice or disclaimer, and Applicant reserves the right to pursue any canceled subject matter in one or more applications with the same rights of priority as the instant application. Upon entry of the amendments, claims 26-28, 31-36, and 38-48 will remain pending. These claims are presented for reconsideration.

II. § 103 Rejections

Claims 26-28, 31-34, 36-45 and 47 were rejected under 35 U.S.C. § 103(a) for alleged obviousness over Mauvais-Jarvis in view of Gunther. Claims 26-28, 31-34, 36, 39-45 and 47 were rejected under 35 U.S.C. § 103(a) for alleged obviousness over Mauvais-Jarvis in view of Parab. Claims 35 and 46 were rejected for alleged obviousness over those same references, further in view of U.S. Patent No. 5,720,963 (Smith). Claims 38 and 48 were rejected for alleged obviousness over Mauvais-Jarvis and Gunther or Parab, further in view of U.S. Patent No. 6,013,270 (Hargraves). Applicant respectfully traverses these rejections.

The instant claims recite pharmaceutical compositions for percutaneous administration comprising 4-hydroxy tamoxifen and about 0.5% to 2% by weight of isopropyl myristate (claims 26-28, 31-36 and 38), or comprising a pharmaceutically active agent and about 0.5% to 2% by weight of isopropyl myristate, wherein the pharmaceutically active agent consists of 4-hydroxy tamoxifen (claims 39-48). The cited references do not teach or suggest such a composition.

The premise behind the obviousness rejections is that the disclosure of the use of a fatty acid ester as a penetration enhancer in any percutaneous composition (e.g., Gunther or Parab) renders obvious the specific composition at issue, which comprises 4-hydroxy tamoxifen and a specific fatty acid ester penetration enhancer, isopropyl myristate. This

premise, however, is not scientifically sound. As explained previously, the ability of a particular penetration enhancer to be effective for a particular active agent in a particular formulation is unpredictable.

For example, Takahashi *et al.*, *Biol. Pharm. Bull.* 28: 870-75 (2005) (copy attached), reports that isopropyl myristate was not an effective penetration enhancer for a percutaneous composition comprising propofol as the active agent. As summarized in the "Discussion" at page 873, even though isopropyl myristate was "known to be a useful lipophilic solvent for transdermal absorption, . . . a significant enhancing effect was not observed after treatment with a mixture of [propofol] and [isopropyl myristate.]" This article evidences that, despite the theoretical usefulness of isopropyl myristate as a penetration enhancer, it did not prove useful in the specific composition at hand.

Of further interest is the authors' explanation of the poor enhancing effect of isopropyl myristate. In particular, they state that release of the propofol from the composition was suppressed because of the affinity between the propofol and the isopropyl myristate, which both are lipophilic. *See, e.g.,* Takahashi at 873-74. The active agent recited in the instant claims, 4-hydroxy tamoxifen, also is lipophilic. Thus, these teachings in Takahashi would discourage the skilled artisan from using a lipophilic penetration enhancer, such as isopropyl myristate, as a penetration enhancer for 4-hydroxy tamoxifen. This teaching away from the present invention further undermines the obviousness rejection.

Numerous other publications evidence the unpredictability of formulating effective percutaneous compositions, particularly with regard to the choice of penetration enhancer. For example, Sekine *et al.*, *Drug Design & Delivery* 1: 245-52 (1987) (copy attached), reports that azone was an effective absorption promoter for a transdermal hydroalcoholic gel composition comprising verapamil as the active agent, whereas isopropyl myristate was not. As reported in the Abstract, where azone increased plasma levels of verapamil by as much as ten-fold, isopropyl myristate had no effect on plasma levels, although it did appear to increase local transdermal absorption.

Lee *et al.*, Int'l J. Pharm. 33-39 (2006) (copy attached), reports that while isopropyl myristate was somewhat effective as a penetration enhancer for a percutaneous lidocaine composition, a combination of n-methyl pyrrolidone and isopropyl myristate enhanced drug flux 25 times greater than isopropyl myristate alone, and 4 times greater than n-methyl pyrrolidone alone.

Bergonzi *et al.*, Pharmazie 60: 3638 (2005) (copy attached), assessed the effects of "[f]ive well-known penetration enhancers" on the permeation of sesquiterpenes, and reports that no sesquiterpene permeation was detected when isopropyl myristate was used as the enhancer. In contrast, oleic acid and dimethylsulfoxide were found to be effective penetration enhancers for sesquiterpenes. *See e.g.,* Bergonzi, page 37, Table 3.

These articles evidence that those skilled in the art would not consider the disclosure of the usefulness of a fatty acid ester as a penetration enhancer in one percutaneous composition to suggest that the same penetration enhancer would be useful in a different composition, comprising a different formulation or active agent. Thus, those skilled in the art would not understand from Gunther or Parab that isopropyl myristate would be an effective penetration enhancer for a percutaneous composition comprising 4-hyroxy tamoxifen, as claimed.

As further evidence of the unpredictability in this art, Applicant submits herewith a Declaration under 37 CFR § 1.132 by Valérie Masini-Etévé, Ph.D. As noted in the Declaration, Dr. Masini-Etévé is Head of Non Clinical R&D at Laboratoires Besins-International, the assignee of the captioned application. The results reported in Sections III and IV of Dr. Masini-Etévé's declaration demonstrate the unpredictability and performance variability associated with transdermal compositions in general, and with penetration enhancers in particular. The data presented by Dr. Valérie Masini-Etévé show that two known penetration enhancers, oleic acid and isopropyl myristate, have unpredictable effects on permeation, depending, for example, on the active agent. As shown in Section III, oleic acid is not an effective penetration enhancer for 4-OHT, while isopropyl myristate is effective. As shown in Section IV, isopropyl myristate is not a particularly effective penetration enhancer for progesterone, while oleic acid is more effective. As explained by

Dr. Masini-Etévé, this unpredictability means that it is not possible to modify a given composition to replace the penetration enhancer with a different penetration enhancer, and reasonably predict that the modified composition will perform equivalently to the original composition. Instead, the suitability of a particular penetration enhancer must be determined experimentally for a given composition or active agent.

Mauvais-Jarvis & Gunther

The instant claims are further distinguished from Mauvais-Jarvis and Gunther. For example, although Gunther was cited for teaching the use of fatty acid esters as a penetration enhancer for steroid hormones, the Examiner should recognize that Gunther uses fatty acid esters as solvents in its compositions. *See, e.g.*, Gunther, page 1, paragraph 7 ("The concentration in which the steroid hormone . . . are optionally dissolved in the fatty acid ester . . . ."). Thus, the compositions of Gunther are comprised mostly of fatty acid esters, and Gunther exemplifies compositions comprising 90% and 98% by weight of isopropyl myristate.

The accompanying declaration of Dr. Masini-Etévé demonstrates that high amounts of isopropyl myristate, such as those taught in Gunther, would not be suitable in the context of the hydroalcoholic gel compositions recited in the instant claims. Indeed, the results reported in Section I of the Masini-Etévé declaration show that amounts of isopropyl myristate well-below those taught in Gunther would be disadvantageous in the context of hydroalcoholic gel compositions. This is because the solubility of isopropyl myristate in hydroalcoholic gel compositions is limited, and isopropyl myristate concentrations greater than about 2.0% (w/w) lead to problems, such as phase separation, that make the composition unsuitable.

Thus, compositions of Gunther, which use isopropyl myristate as a solvent, in no way teach or suggest compositions comprising only about 0.5% to 2.0% by weight isopropyl myristate, as recited in the instant claims. Indeed, there is no teaching or suggestion in the combination of Mauvais-Jarvis and Gunther that a composition comprising only about 0.5% to 2.0% by weight isopropyl myristate would be useful for percutaneous delivery.

Moreover, the rejection based on Mauvais-Jarvis and Gunther alleges that because the Mauvais-Jarvis composition includes both 4-OHT and progesterone, someone skilled in the art would have been motivated to use the penetration enhancer taught by Gunther for steroid hormones in the Mauvais-Jarvis composition. As noted above, however, and as shown in Dr. Masini-Etévé's declaration, isopropyl myristate is not a particularly effective penetration enhancer for progesterone. Indeed, while Gunther mentions steroid hormones generally, progesterone is not included in its list of steroid hormones that are suitable for use in its compositions. Thus, the skilled artisan would not have been motivated by Gunther to use isopropyl myristate in a composition comprising progesterone, such as Mauvais-Jarvis discloses.

For at least the foregoing reasons, Applicant respectfully requests reconsideration and withdrawal of the § 103 rejection based Mauvais-Jarvis and Gunther.

Mauvais-Jarvis and Parab

The instant claims likewise are further distinguished from Mauvais-Jarvis and Parab. Parab is directed to transdermal compositions comprising dibutyl adipate, or a combination of dibutyl adipate and isopropyl myristate, as enhancers. While Parab states generally that the concentration of isopropyl myristate may be from 0 % wt to 99.9 % wt, with the "more preferred" range being from 1% wt to 30% wt, these broad teachings in no way suggest the specific compositions of the present invention, which include about 0.5 % wt to 2.0 % wt isopropyl myristate. Moreover, the examples in Parab use compositions comprising 3% wt, 6% wt, and 10% wt isopropyl myristate, which would lead the skilled artisan to compositions comprising much higher amounts of isopropyl myristate than recited in the instant claims.

As noted above, the accompanying declaration of Dr. Masini-Etévé supports the importance of the recited amounts of isopropyl myristate in the context of the hydroalcoholic gel compositions recited in the instant claims.

The results reported in Section I of the Masini-Etévé declaration show that large amounts of isopropyl myristate, such as the 3% wt, 6% wt, or 10% wt isopropyl myristate exemplified in Parab, would be disadvantageous in the context of the hydroalcoholic gel

compositions of the present invention. This is because the solubility of isopropyl myristate in hydroalcoholic gel compositions is limited, and isopropyl myristate concentrations greater than about 2.0% (w/w) lead to problems, such as phase separation, that make the composition unsuitable.

The results reported in Section II of the Masini-Etévé declaration show that isopropyl myristate is an effective penetration enhancer at concentrations much lower than those exemplified in Parab, and at concentrations lower than the lowest end of Parab's "more preferred" range of isopropyl myristate (1% wt to 30% wt). In particular, the data show that isopropyl myristate is an effective penetration enhancer for 4-OHT when used at concentrations below 1.0%, including at 0.5%, 0.7%, and 0.9%.

Because Parab provides no guidance that would lead a skilled artisan to a composition comprising about 0.5 % wt to 2.0 % wt isopropyl myristate, Applicant respectfully requests reconsideration and withdrawal of the § 103 rejection based on Mauvais-Jarvis and Parab.

For at least the foregoing reasons, the obviousness rejections of claims 26-28, 31-34 and 36 should be withdrawn. The rejections of claims 35, 46, 38 and 48 rely on Mauvais-Jarvis and Gunther or Parab to suggest the compositions recited in claims 26 or 39, from which these claims depend. Because no combination of Mauvais-Jarvis, Gunther and Parab suggests the compositions recited in claims 26 and 39, and because neither Smith nor Hargraves remedy the deficiencies of the primary references, the obviousness rejections of claims 35, 46, 38 and 48 likewise should be withdrawn.

CONCLUSION

Applicant submits that this application is in allowable condition, and an early indication to this effect is requested. If the Examiner believes that any issue requires further consideration, she is invited to contact the undersigned directly.

The Commissioner is authorized to charge any additional fees, which may be required regarding this application under 37 CFR §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the

Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of concurrently submitted papers, then Applicant petitions for such extension, under 37 CFR §1.136, and authorizes payment of the relevant fee(s) from the deposit account.

Respectfully submitted,

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